201-15019B

ROBUST SUMMARY
OF INFORMATION ON

Substance Group **GREASE THICKENERS**

Summary prepared by American Petroleum Institute

Creation date: October 11, 2003

Printing date: December 30, 2003

Date of last Update: **December 29, 2003**

Number of pages: **33**

NB. Reliability of data included in this summary has been assessed using the approach described by Klimisch et al.

Klimisch, H. J., Andreae, M. and Tillman, U, (1997)
A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data.
Regulatory Toxicology and Pharmacology 25, 1-5.

1. General Information

Id Greases
Date 12. 24 .2003

2.1 MELTING POINT

Method : Calculated by MPBPWIN, V1.40 subroutine in EPIWIN V3.10 computer model (EPA 2000)
GLP : No
Test Substance :
Remark : The members of the grease thickeners category are composed of various salts of fatty acids containing hydrocarbon chains of 9 to 22 carbon atoms. The melting point estimates given here are for fatty acid salts covering this range of carbon atoms. The data represent a potential melting point range for all substances in the grease thickeners category.

Result :

	Molecular Weight	No. C Atoms	Estimated MP Value, °C
Lithium Salts			
nonanedioic acid, dilithium salt	200.09	9	186
octadecanoic acid, lithium salt	290.42	18	249
octadecanoic acid, 12-hydroxy-stearate, lithium salt	306.42	18	264
docosanoic acid, lithium salt	346.53	22	271
Calcium Salts			
octadecanoic acid, 12-hydroxy, calcium salt	639.03 [1]	36	320
stearic acid, calcium salt	607.04 [1]	36	288

[1] Compound composed of two fatty acid molecules attached to calcium.

Reliability : (2) Reliable with restrictions
Estimated melting points were calculated using a validated computer model.
: (17)

2.2 BOILING POINT

Method : Calculated by MPBPWIN, V1.40 subroutine in EPIWIN V3.10 computer model (EPA 2000)
GLP : No
Test Substance :
Remark : The members of the grease thickeners category are composed of various salts of fatty acids containing hydrocarbon chains of 9 to 22 carbon atoms. The boiling point estimates given here are for fatty acid salts covering this range of molecular weights and number of carbon atoms. The data represent a potential boiling point range for all substances in the grease thickeners category.

Result :

	Molecular Weight	No. C Atoms	Estimated BP Value, °C
Lithium Salts			
nonanedioic acid, dilithium salt	200.09	9	484
octadecanoic acid, lithium salt	290.42	18	578
octadecanoic acid, 12-hydroxy-stearate, lithium salt	306.42	18	611
docosanoic acid, lithium salt	346.53	22	624
Calcium Salts			
octadecanoic acid, 12-hydroxy, calcium salt	639.03 [1]	36	730
stearic acid, calcium salt	607.04 [1]	36	661

[1] Compound composed of two fatty acid molecules attached to calcium.

Reliability : (2) Reliable with restrictions
Estimated melting points were calculated using a validated computer model.

: (17)

2.3 VAPOUR PRESSURE

Method : Calculated by MPBPWIN, V1.40 subroutine in EPIWIN V3.10 computer model (EPA 2000)

GLP : No

Test Substance :

Remark : The members of the grease thickeners category are composed of various salts of fatty acids containing hydrocarbon chains of 9 to 22 carbon atoms. The vapour pressure estimates given here are for fatty acid salts covering this range of molecular weights and number of carbon atoms. The data represent a potential vapour pressure range for all substances in the grease thickeners category.

Result :

	Molecular Weight	No. C Atoms	Estimated VP Value, hPa
Lithium Salts			
nonanedioic acid, dilithium salt	200.09	9	2×10^{-9}
octadecanoic acid, lithium salt	290.42	18	1×10^{-12}
octadecanoic acid, 12-hydroxy-stearate, lithium salt	306.42	18	2×10^{-16}
docosanoic acid, lithium salt	346.53	22	5×10^{-14}
Calcium Salts			
octadecanoic acid, 12-hydroxy, calcium salt	639.03 [1]	36	1×10^{-21}
stearic acid, calcium salt	607.04 [1]	36	6×10^{-14}

[1] Compound composed of two fatty acid molecules attached to calcium.

Reliability : (2) Reliable with restrictions
Estimated melting points were calculated using a validated computer model.

: (17)

2.4 PARTITION COEFFICIENT

Method : Calculated by MPBPWIN, V1.40 subroutine in EPIWIN V3.10 computer model (EPA 2000)
GLP : No
Test Substance :
Remark : Because fatty acids are ionizable compounds, Kow measurements (hence log P) can vary greatly with pH. The variation depends upon pH and the pKa of the compound. In general, Kow values of a compound are lower when it exists predominantly in the ionized form as compared to existing primarily in the non-ionized form. The KOWWIN V1.66 model handles ion pairs in a special way and gives Kow estimates that are an estimate for the ionized acid. Many fatty acids have pKa values circumneutral, and they would exist predominantly in the molecular form at environmentally relevant pHs. Therefore, the estimates given here are potentially lower than what would be expected for the salt form at typical environmental pHs.

Result :

	Molecular Weight	No. C Atoms	Estimated Log Kow
Lithium Salts			
nonanedioic acid, dilithium salt	200.09	9	-3.56
octadecanoic acid, lithium salt	290.42	18	4.13
octadecanoic acid, 12-hydroxy-stearate, lithium salt	306.42	18	2.60
docosanoic acid, lithium salt	346.53	22	6.10
Calcium Salts			
octadecanoic acid, 12-hydroxy, calcium salt	639.03 [1]	36	11.7
stearic acid, calcium salt	607.04 [1]	36	14.3

[1] Compound composed of two fatty acid molecules attached to calcium.

Reliability : (2) Reliable with restrictions
Estimated melting points were calculated using a validated computer model.
: (17)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water
Method : Calculated by MPBPWIN, V1.40 subroutine in EPIWIN V3.10 computer model (EPA 2000)
GLP : No
Test Substance :
Remark : The members of the grease thickeners category are composed of various salts of fatty acids containing hydrocarbon chains of 9 to 22 carbon atoms. The water solubility estimates given here are for fatty acid salts covering this range of molecular weights and number of carbon atoms. The data represent a potential water solubility range for all substances in the grease thickeners category.

Result :

	Molecular Weight	No. C Atoms	Estimated Solubility, mg/l
Lithium Salts			
nonanedioic acid, dilithium salt	200.09	9	1×10^{6}
octadecanoic acid, lithium salt	290.42	18	4.1
octadecanoic acid, 12-hydroxy-stearate, lithium salt	306.42	18	0.1
docosanoic acid, lithium salt	346.53	22	0.04
Calcium Salts			
octadecanoic acid, 12-hydroxy, calcium salt	639.03 [1]	36	9.7×10^{-9}
stearic acid, calcium salt	607.04 [1]	36	8.2×10^{-11}

[1] Compound composed of two fatty acid molecules attached to calcium.

Reliability : (2) Reliable with restrictions
Estimated melting points were calculated using a validated computer model.

: (17)

3.1.1 PHOTODEGRADATION

3.1.2 STABILITY IN WATER

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

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4.1 ACUTE/PROLONGED TOXICITY TO FISH

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4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

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4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD_{50}
Value	:	> 5000 mg/kg bw
Species	:	Rat
Strain	:	Sprague-Dawley
Sex	:	Male/female
Number of animals	:	10
Vehicle	:	Undiluted
Doses	:	5000 mg/kg only
Year	:	1994
GLP	:	Yes
Test substance	:	Grease Starplex 2 Starplex 2 is a grease with the following composition Wt % base oil ~65 Thickeners Li 12-hydroxy stearate 13.1% Dilithium azelate 2.6% Wt % other additives ~20
Method	:	Five male and five female fasted rats were given a single oral dose (5000 mg/k) of the test material. The rats were observed 1, 4 and 24 hours after administration of the test material for clinical signs of toxicity and any other pharmacological signs. Body weights were recorded before administration of the test material and again on days 7 and 14. All animals were sacrificed on day 14 and a gross necropsy was performed on each of them. Abnormal observations were recorded.
Result	:	No clinical signs were observed and no animal died during the study. There was a body weight increase for all animals on the study. At necropsy there were no abnormal observations. The LD_{50} of the test material was greater than 5000 mg/kg.
Reliability	:	(1) valid without restriction

(12)

Type	:	LD_{50}
Value	:	> 10000 mg/kg bw
Species	:	Rat
Strain	:	Albino
Vehicle	:	Corn oil
Doses	:	0.05-10.0 g/kg
Year	:	1982
GLP	:	No data
Test substance	:	Magnesium stearate
Result	:	The publication states: Given as 25% suspension in corn oil. Animals fasted overnight and then given dose ranging from 0.05 to 10.0 g/kg. Animals observed daily for 14 days. All animals at 10.0 g/kg exhibited mild diarrhea.
Reliability	:	(4) not assignable Information is taken from the report of a Cosmetic ingredient review panel. Original data not available.

(2)

Type	:	LD_{50}
Value	:	5000 - 15000 mg/kg bw
Species	:	Rat
Strain	:	Albino
Vehicle	:	Propylene glycol
Doses	:	0.05, 1, 3 & 15 g/kg
Year	:	1982
GLP	:	No data
Test substance	:	Lithium stearate
Result	:	Lithium stearate was administered in propylene glycol (concentration unspecified) to 30 albino rats (sex not specified). The publication states: Animals fasted for 24 hrs. and then given dosages ranging from 0.05 to 15.0 g/kg. Animals dosed at 0.05, 1.0 and 3.0 g/kg showed no toxic effects; all animals administered 15.0 g/kg died within 16 hrs. having exhibited unkempt coats, impaired locomotion and lethargy prior to death.
Reliability	:	(4) not assignable Information is taken from the report of a Cosmetic ingredient review panel. Original data not available.

(2)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD_{50}
Value	:	> 3000 mg/kg bw
Species	:	Rabbit
Strain	:	New Zealand white
Sex	:	Male/female
Number of animals	:	10
Vehicle	:	Undiluted
Doses	:	300 mg/kg
Method	:	
Year	:	1994
GLP	:	Yes
Test substance	:	Grease Starplex 2 Starplex 2 is a grease with the following composition Wt % base oil ~65 Thickeners Li 12-hydroxy stearate 13.1% Dilithium azelate 2.6% Wt % other additives ~20
Method	:	Undiluted test material was applied to the shorn dorsal skin of five male and five female NZW rabbits. The applied grease was covered with an occlusive dressing which was left in place for 24 hours. Following the 24 hours exposure period the covering was removed and any residual test material was wiped from the skin using mineral oil and a gauze. Observations were recorded daily throughout the following 14 days. Body weights were recorded prior to application of the test material and again on days 7 and 14. All rabbits were killed by lethal injection and a gross necropsy was performed and a record made of any abnormalities.
Result	:	There were no clinical signs of toxicity during the study and no animals

died. Erythema and edema was observed at the treated skin site when the occlusive covering was removed. At this time average erythema and edema scores were 2.6 and 2 respectively (same average scores for each sex). The skin responses gradually subsided and by day 6 had completely disappeared. Animals gained weight during the study and no abnormalities were observed at necropsy.
The dermal LD_{50} was therefore greater than 3000 mg/kg.

Reliability : (1) valid without restriction

(11)

5.2.1 SKIN IRRITATION

Species : Rabbit
Concentration : Undiluted
Exposure : Semi occlusive
Exposure time : 4 hour(s)
Number of animals : 6
Vehicle : None
Year : 1944
GLP : Yes
Test substance : Grease Starplex 2
Starplex 2 is a grease with the following composition

Wt % base oil	~65
Thickeners	
Li 12-hydroxy stearate	13.1%
Dilithium azelate	2.6%
Wt % other additives	~20

Method : 0.5 ml of undiluted test material was applied to three separate sites on the shorn dorsal trunks of three male and three female NZW rabbits. Each site was covered with a semi occlusive dressing. One site was abraded, the other two were intact skin.
One of the intact skin sites was only covered for 4 hours and the other two sites were covered for 24 hours. At the end of the exposure periods, residual test material was removed from the skin using gauze and mineral oil.
After patch removal, the test site was examined for erythema and edema and the responses were scored immediately using the standard Draize scale. Skin responses were scored again at 1, 24, 48 and 72 hours after patch removal and again on days 4 through 6.
Body weights of animals were recorded before application of test material and again at the end of the study.

Result : No clinical signs of toxicity were observed and all animals gained weight over the course of the study.
Average scores for erythema and edema are as shown in the following table.

Time	**4 hour**		**24 hour exposure**			
	Erythema	**Edema**	**Erythema**		**Edema**	
			I*	A	I	A
0 hrs	0.7	0	3.2	3.2	2.7	2.8
1 hr	0.7	0	3.2	3.2	2.7	2.8
24 hrs	0.2	0.2	3	3.2	2.3	2.3
48 hrs	0.2	0.2	2	2.2	1.7	2

72 hrs	0.2	0	1.5	1.7	1.3	1.5
Day 4	0	0	1	1	0.5	0.7
Day 5			0.2	0.2	0	0
Day 6			0	0	0	0

* I = Intact, A = Abraded

The four hour exposures resulted in only slight irritation which had cleared by day 4.

24 hour exposure caused moderate to severe erythema with well defined to severe edema. Skin responses had cleared by day 6 and there was no evidence that abraded skin was more irritated than intact skin.

The calculated Primary irritation indices were:
4 hour exposure 0.38
24 hour exposure 4.92

Reliability : (1) valid without restriction

(13)

Species : Rabbit
Concentration : Undiluted
Exposure time : 4 hour(s)
Number of animals : 6
Vehicle : None
PDII : 0
Result : Not irritating
Year : 1982
GLP : No data
Test substance : Magnesium stearate

Method : Two studies were summarized:
A four hour study of acute dermal corrosion and a 24 hour study for skin irritation.
In both studies 6 albino rabbits were used.
The test material was applied under an occlusive dressing in both studies.
Also in both studies half the test sites were abraded while the other half were intact skin.

The corrosion study was conducted according to the procedure described in 49 CFR 173.240 (a) (1).

Result : The primary irritation index in both studies was 0.
Reliability : (4) not assignable
Information is taken from the report of a Cosmetic ingredient review panel.
Original data not available.

(2)

5.2.2 EYE IRRITATION

Species : Rabbit
Concentration : Undiluted
Dose : 0.1 ml
Number of animals : 6
Vehicle : None
Year : 1994
GLP : Yes

Test substance : Grease Starplex 2
Starplex 2 is a grease with the following composition

Wt % base oil	~65
Thickeners	
Li 12-hydroxy stearate	13.1%
Dilithium azelate	2.6%
Wt % other additives	~20

Method : 0.1 ml of test material was placed in the conjunctival sac of the right eye of six female NZW rabbits. The left eye was untreated and served as control. The eyes were examined at 1, 24, 48 and 72 hours after treatment and again on day 7. Ocular reactions were scored according to the standard Draize scale.
Body weights were recorded at the beginning and the end of the study.

Result : Conjunctival redness was observed in all animals 1 hour after application of the test material and in three animals at 24 hours. This conjunctival response continued in one animal for 72 hours but was not seen in any animal after 7 days.
Iritis was observed in only one animal at 24 hours and corneal opacity also occurred at 24 hours in the same animal and this persisted for 24 hours. All eyes were normal after 7 days.

The average Draize scores for 6 rabbits are shown in the following table.

Time after application of test material	Cornea	Iris	Conjunctivae
1 hour	0	0	10
24 hours	0.8	0.8	3.3
48 hours	0.8	0	2.7
72 hours	0	0	1.3
7 Days	0	0	0

Reliability : (1) valid without restriction

(14)

Species : Rabbit
Concentration : Undiluted
Comment : Not rinsed
Number of animals : 6
Vehicle : None
Result : Not irritating
Year : 1982
GLP : No data
Test substance : Magnesium stearate

Result : The scores were zero on days 1, 2 and 3
Reliability : (4) not assignable
Information is taken from the report of a Cosmetic ingredient review panel. Original data not available.

(2)

5.3 SENSITIZATION

Type : Buehler Test
Species : Guinea pig
Concentration : 1st: Induction undiluted occlusive epicutaneous
2nd: Induction undiluted occlusive epicutaneous
3rd: Induction undiluted occlusive epicutaneous
Number of animals : 10
Vehicle : None
Result : Not sensitizing
Year : 1997
GLP : Yes
Test substance : Starplex MPGM
Starplex MPMG 2 is a grease with the following composition

Wt % base oil	~80
Thickeners	
Li 12-hydroxy stearate	8.8%
Dilithium azelate	1.8%
Wt % other additives	~10

Method : On the basis of the results of a preliminary irritation screen, it was decided to use undiluted test material for the induction and challenge dosing in the sensitization test.
The test material was applied under a Hilltop chamber to the shorn skin of 10 male and 10 female Guinea pigs. The patches were allowed to remain in place for six hours, after which they were removed and any residual test material was also removed from the skin using a gauze and mineral oil.
The treated sites were examine after each dosing day and scored for dermal irritation at 24 and 48 hours. This dosing and scoring procedure was performed once a week for three weeks.
A concurrent positive control group of five animals (3 males and 2 females) was treated with 0.3% 1-chloro-2,4-dinitrobenzene in 80% ethanol (ethanol in distilled water).
An additional group of ten animals (5 of each sex) was treated with vehicle (mineral oil).

Fourteen days after the last induction dose, the animals were challenged by applying material in the same manner as the induction applications but on a naive site.
The vehicle control group was challenged with mineral oil and test substance.
The positive control group animals were challenged with DNCB at 0.01% and 0.2% in acetone.
All animals were observed for local and systemic effects.
24 hours after challenge, the animals were depilated. After a minimum of 2 hours following depilation the test sites were assesed and graded (24 hour grade) and were graded again after a further 24 hours (48 hour grade).

When skin reactions were graded throughout the study scores were attributed to each test site on a scale of 0-3 for erythema.
After the sensitization doses a score of 1 or more was taken to indicate that sensitization had occured. Furthermore if the test reactions exceeded the most severe control reactions, the animal was considered to be sensitized.

Result : A summary of the challenge scores is given in the following table.

Test	**% animals with score at 24 hours**				
Group	**0**	**+**	**1**	**2**	**3**
Vehicle control Induced with mineral oil					

Mineral oil challenge	100	0	0	0	0
Test material challenge	100	0	0	0	0
Test material induced with neat test material					
Test material challenge	100	0	0	0	0
Positive control animals induced with 0.3% DNCB					
0.01% DNCB challenge	60	20	20	0	0
0.2% DNCB challenge	0	0	20	0	80

The positive control data clearly demonstrate the sensitivity of the test method. The test material itself did not cause skin sensitization in this study.

Test substance :
Reliability : (1) valid without restriction

(15)

5.4 REPEATED DOSE TOXICITY

Type : Sub-chronic
Species : Rat
Sex : Male/female
Strain : Wistar
Route of admin. : Oral feed
Exposure period : 3 Months
Frequency of treatm. : Daily in the diet
Doses : 5, 10 & 20% in the diet
Control group : Yes
NOAEL : 5 %
Year : 1980
GLP : No data
Test substance : Magnesium stearate

Method : Groups of 20 male and 20 female six week old rats were fed diets containing 5, 10 or 20 magnesium stearate. The diets were semi synthetic in which sodium caseinate replaced casein. The carbohydrates of the diet were substituted by magnesium stearate as follows:

Group	Magnesium stearate % in diet	Carbohydrate % in diet
Contro l	0	67.3
	5	62.3
	10	57.3
	20	47.8

The diets fed were considered isocaloric, as stearate has a calorific value of about 9, and a pilot study demonstrated that 35-40% of the stearate is absorbed at a 10% level in the diet. Acidified water (pH 3.5) was available ad libitum.
The animals were weighed once weekly and food utilization and weight gain was calculated for each sex of all groups of rats.
Blood samples were taken from 8 males and 8 females from each group prior to dosing and at 8 and 12 weeks. The following hematological and clinical chemistry determinations were made:

Hematology
Hemoglobin
packed cell volume (PCV)
red cell count

total white cell count
reticulocyte count
differential white cell count.

Clinical chemistry
Glucose
urea
aspartate amino transferase
alkaline phosphatase
At the termination of the study, the rats were sacrificed and the following organs were weighed: thymus, liver, kidneys, adrenals, testes/ovaries, heart, lungs, brain and pituitary.
Samples of the organs listed above and the following tissues were taken for light microscopy: urinary bladder, stomach, duodenum, pancreas, jejunum, cecum, colon, thyroid, parathyroid, triceps, brachial muscle, ischiadic nerve, axillar lymph node, uterus, sternum, eye, Harderian gland, skin and submandibular gland. Microscopic examination was undertaken on the high dose and control animals only.

Result **:** The weight gains of the 20% males were significantly less than he corresponding controls during the first 8 weeks of the study [No actual data given in the publication]. Concomitantly these animals were quiet with slow and unsteady movements. Four males in his group died within the first 2 months and all had stone formation in the lower urinary pathways and the deaths were considered to be related to this finding. One other male in this group was incontinent. In the remaining males, the symptoms receded during the following 4 weeks. There were no clinical effects in females in any group.
A reduction in PCV [P<0.01, but no data provided] was found in the 20% males compared to controls. No other hematological differences were reported.
In addition to the findings reported in the males that died in the 20% group, changes were also found in the renal pelvis and in the lower urinary pathways (due to stone formation) at autopsy in 4 males and one female in the 20 % group.
The relative liver and kidney weights recorded were as follows:

Dietary concentration	**Sex**	**Liver g/100g body wt ±SD**	**Kidney g/100g body wt. ±SD**
0	M	3.25±0.21	633±48.6
5	M	3.13±0.21*	614±51.5
10	M	2.99±0.23***	599±40.6*
20	M	2.82±0.18***	640±80.7
0	F	3.30±0.24	768±103
5	F	3.33±0.18	661±86.5***
10	F	3.31±0.31	667±54.0***
20	F	3.16±0.23*	646±55.8***

* P< 0.05
*** P<0.001

Nephrocalcinosis was seen in all females and in 12/20 males in the control group. In 18 of the females nephrocalcinosis was regarded as severe. Slight to moderate nephrocalcinosis was observed in 19/20 of the females in the 20% group and 7/20 of the males were affected only slightly.

Deposition of iron was found in various amounts in kidney and in liver, the amount was increased in the liver of both sexes in the 20% group.
Liver glycogen showed a marked decrease in males in the 20% group and no difference was found in the females.

The authors comment that :

the occurrence of nephrocalcinosis is a common finding in animals fed semi-synthetic diets. The increased magnesium content of the diet could explain the reduction of nephrocalcinosis in the 20% animals. A high magnesium content of the diet has also been previously associated with a greater incidence of stone formation in the lower part of the urinary tract.

The authors concluded that:

when liver weight was used as a measure of adverse effect, the no effect level was estimated to be 5% magnesium stearate in the diet, corresponding to 2500 mg/kg body weight.

Reliability : (2) valid with restrictions
Few experimental details are provided and detailed results are not included in the publication.
However, the publication does provide useful information on the effects of repeated oral exposure to magnesium stearate.

(16)

Type : Sub-chronic
Species : Rat
Sex : Male/female
Strain : Sprague-Dawley
Route of admin. : Gavage
Exposure period : 90 days
Frequency of treatm. : Daily, seven days each week
Doses : 250, 500 & 1000 mg/kg/day
Control group : Yes, concurrent vehicle
NOAEL : 1000 mg/kg
Year : 1977
GLP : Yes
Test substance : R960002575
R960002575 is a code number for Starplex MPMG 2, which is a grease with the following composition

Wt % base oil	~80
Thickeners	
Li 12-hydroxy stearate	8.8%
Dilithium azelate	1.8%
Wt % other additives	~10

The test material was prepared as solutions in corn oil at the following concentrations to achieve the desired dose levels.

Group	Dose group mg/kg/day	Concentration mg/ml	Volume ml/kg
I	0	0	4
II	250	62.5	4
III	500	125	4
IV	1000	250	4

Method : Sprague-Dawley rats were used in this study. The animals (males and females) were aged 6 weeks at the beginning of the study.
The test material was administered orally by gavage at doses of 250, 500 or 1000 mg/kg/day in a dose volume of 4 ml/kg to groups of ten male and ten females for each dose level. Additionally, a group of ten male and ten females served as vehicle controls and for these corn oil alone (4ml/kg) was administered. This treatment was continued daily, seven days each week for 90 days.

Animals were observed twice daily for clinical signs of toxicity. A more thorough examination was undertaken weekly and this included a detailed physical examination for signs of local or systemic toxicity, pharmacological effects and palpation for tissue masses.
Body weights and food intakes were recorded weekly.
At the end of the study, on day 91, and after overnight fasting, animals were killed and blood samples were collected for the following hematological and serum chemistry investigations.

Hematology
Hemoglobin concentration
Hematocrit
Erythrocyte count
Platelet count
Reticulocyte count
Mean corpuscular volume
Mean corpuscular hemoglobin
Mean corpuscular hemoglobin concentration
Prothrobin time
Activated partial thromboplastin time
Total and differential leukocyte counts
Erythrocyte morphology
Reticulocyte count

Clinical chemistry
Aspartate aminotransferase
Alanine aminotransferase
Alkaline phosphatase
Blood urea nitrogen
Fasting glucose
Total protein
Albumin
Globulin (calculated)
A/G ratio (calculated)
Creatinine
Total bilirubin
Sodium
Potassium
Chloride
Calcium
Inorganic phosphorus
Gamma-glutamyl transferase

A complete post mortem examination was performed on all animals. This included an examination of the external surface and all orifices; the external surfaces of the brain and spinal cord; the organs and tissues of the cranial, thoracic, abdominal and pelvic cavities and neck; and the remainder of the carcass.

The following organs were weighed:
Adrenal glands, brain, kidneys, testes with epididymides, liver and ovaries.

The following tissues were preserved and processed for histological examination.
Adrenal glands (2)
Aorta
Bone (sternum/femur with articular surface)
Brain (medulla/pons, cerebrum and cerebellum)
Epididymis (2)
Esophagus
Eye with optic nerve*
Heart
Kidneys (2)
Large intestine (cecum, colon and rectum)
Lacrimal gland*
Liver (2 sections)
Lung with mainstem bronchi
Lymph node (mediastinal)
Lymph node (mesenteric)
Mammary gland*
Muscle (biceps femoris)*
Nasal turbinates
Nerve (sciatic)
Ovaries (2)
Pancreas
Pituitary
Prostate
Salivary gland (submaxillary)
Seminal vesicles
Skin (treated and untreated)
Small intestine (duodenum, ileum and jejunum)
Spinal cord (cervical, thoracic, lumbar)*
Spleen
Stomach
Testes
Thymic region
Thyroid (with parathyroids)
Trachea
Urinary bladder
Uterus (body/horns with cervix)
Zymbal's gland*
Macroscopic lesions
Target organs
All the above tissues from all the animals in the high dose group and the controls were examined microscopically, except those indicated * which were preserved but not examined.

Statistical analysis
Body weight, body weight change fom week 0, food consumption, hematology and clinical chemistry parameters, terminal organ and body weights and organ/body weight ratios and organ/brain weight ratios were analyzed. Mean values of all dose groups were compared to control at each time interval.
A Bartlett's test was performed to determine if groups had equal variance. If the variances were equal, parametric procedures were used; if not,

nonparametric parametric procedures were used.

The parametric procedures were the standard one way ANOVA using the F distribution to assess significance. If significant differences among the means were indicated, Dunnett's test was used to determine which means were significantly different from control. If a nonparametric procedure for testing equality of means was needed, the Kruskal-Wallis test was used, and if differences were indicated a summed rank test (Dunn) was used to determine which treatments differed from control.

A statistical test for trend in the dose levels was also performed. In the parametric case, standard regression techniques with a test for trend and lack of fit were used. In the nonparametric case Jonckheere's test for monotonic trend was used.

The test for equal variance (Bartlett's) was conducted at the 1% two-sided risk level. All other statistical tests were conducted at the 5% and 1%, two-sided risk level.

Result : There were no mortalities during the study and there were no treatment-related clinical signs of toxicity. There were no adverse effects of treatment observed during the ophthalmoscopic examinations. Body weights were unaffected by treatment. The food consumption values for the 500 and 1000 mg/kg groups were often higher than the controls. However, they were considered to be within normal ranges and not treatment-related.

All except the following hematological parameters were unaffected by treatment. Those listed below were within the normal range for the laboratory and were not considered to be of toxicological significance.
Prothrombin time increases in males only:
15% in 500 mg/kg/day group
19% in 1000 mg/kg/day group
Activated partial thromboplastin time increase
18% in 250 and 1000 mg/kg/day groups

The only difference in clinical chemistry was a 9% increase in the phosphate levels of the 500 mg/kg/day females. This difference was not considered to be a treatment-related effect.

There were no effects on either organ weights, organ/body weight ratios or organ/brain weight ratios.

There were no macroscopic findings at necropsy and no treatment-related microscopic findings.

The NOAEL was considered to be 1000 mg/kg/day.

Test substance :
Reliability : (1) valid without restriction

(5)

Type : Sub-acute
Species : Rat
Sex : Male/female
Strain : Sprague-Dawley
Route of admin. : Dermal
Exposure period : Six hours daily
Frequency of treatm. : Daily, five days each week for four weeks
Post exposure period :

Doses : 525, 1050 & 2100 mg/kg/day
Control group : Yes, concurrent vehicle
NOAEL : 2100 mg/kg bw
Method :
Year : 1977
GLP : Yes
Test substance : TS: R960002575
R960002575 is a code number for Starplex MPMG 2, which is a grease with the following composition

Wt % base oil	~80
Thickeners	
Li 12-hydroxy stearate	8.8%
Dilithium azelate	1.8%
Wt % other additives	~10

The test material was prepared as solutions in corn oil at the following concentrations to achieve the desired dose levels.

Group	Dose group mg/kg/day	Concentration mg/ml	Volume ml/kg
I	0	0	4
II	250	62.5	4
III	500	125	4
IV	1000	250	4

Method : Male and female Sprague-Dawley rats aged approximately 7 and 9 weeks respectively were used in this study.
The test material was applied to the shorn skin of groups of five male and five females for each dose level. Additionally, a group of five male and five females served as vehicle controls and for these mineral oil alone was applied. The test sites were covered with an occlusive dressing which was left in place for six hours. After this time, the dressings were removed and any residual test material was removed from the skin using a gauze and mineral oil. This treatment was continued daily, five days each week for four weeks.

Animals were observed twice daily for clinical signs of toxicity. A more thorough examination was undertaken weekly and this included a detailed physical examination for signs of local or systemic toxicity, pharmacological effects and palpation for tissue masses.
Body weights and food intakes were recorded weekly.
At the end of the study, and after overnight fasting, animals were killed and blood samples were collected for the following hematological and serum chemistry investigations.

Hematology
Hemoglobin concentration
Hematocrit
Erythrocyte count
Platelet count
Mean corpuscular volume
Mean corpuscular hemoglobin
Mean corpuscular hemoglobin concentration
Prothrobin time
Activated partial thromboplastin time
Total and differential leukocyte counts

Erythrocyte morphology
Reticulocyte count

Clinical chemistry
Aspartate aminotransferase
Alanine aminotransferase
Alkaline phosphatase
Blood urea nitrogen
Fasting glucose
Total protein
Albumin
Globulin (calculated)
A/G ratio (calculated)
Creatinine
Totall bilirubin
Sodium
Potassium
Chloride
Calcium
Inorganic phosphorus
Gamma-glutamyl transferase

A complete post mortem examination was performed on all animals. This included an examination of the external surface and all orifices; the external surfaces of the brain and spinal cord; the organs and tissues of the cranial, thoracic, abdominal and pelvic cavities and neck; and the remainder of the carcass.

The following organs were weighed:
Adrenal glands, brain, kidneys, testes with epididymides, liver and ovaries.

The following tissues were preserved and processed for histological examination.
Adrenal glands (2)
Brain (medulla/pons, cerebrum and cerebellum)
Heart
Kidneys (2)
Liver (2 sections)
Ovaries (2)
Skin (treated and untreated)
Spleen
Testes with epididymides (2)

All the above tissues from all the animals in the high dose group and the controls were examined microscopically.

Statistical analysis
Body weight, body weight change from week 0, food consumption, hematology and clinical chemistry parameters, terminal organ and body weights and organ/body weight ratios and organ/brain weight ratios were analyzed. Mean values of all dose groups were compared to control at each time interval.
A Bartlett's test was performed to determine if groups had equal variance. If the variances were equal, parametric procedures were used; if not nonparametric parametric procedures were used.

The parametric procedures were the standard one way ANOVA using the F

distribution to assess significance. If significant differences among the means were indicated, Dunnett's test was used to determine which means were significantly different from control. If a nonparametric procedure for testing equality of means was needed, the Kruskal-Wallis test was used, and if differences were indicated a summed rank test (Dunn) was used to determine which treatments differed from control.

A statistical test for trend in the dose levels was also performed. In the parametric case, standard regression techniques with a test for trend and lack of fit were used. In the nonparametric case Jonckheere's test for monotonic trend was used.

The test for equal variance (Bartlett's) was conducted at the 1% two-sided risk level. All other statistical tests were conducted at the 5% and 1%, two-sided risk level.

Result : All animals survived throughout the study and there were no clinical signs of toxicity and no dermal irritation was observed in the treatment groups.
Body weights were unaffected by treatment except that at four weeks the 2100 mg/kg/day males weighed approximately 3% less than the corresponding controls. However, this difference was not statistically significant.
Food consumption of the treatment groups were generally similar to the controls. A slight increase in food consumption of the mid dose males and high dose females at weeks one and two respectively were not considered to be of biological relevance.
Hematological and clinical chemical parameters, organ weights and microscopic findings were all unaffected by treatment.
It was concluded that the NOAEL was 2100 mg/kg/day.

Reliability : (1) valid without restriction

(6)

Type	:	Sub-chronic
Species	:	Rat
Sex	:	Male/female
Strain	:	Sprague-Dawley
Route of admin.	:	Dermal
Exposure period	:	Six hours daily
Frequency of treatm.	:	Daily, five days each week for 13 weeks
Doses	:	525, 1050 & 2100 mg/kg/day
Control group	:	Yes, concurrent vehicle
NOAEL	:	2100 mg/kg
Year	:	1997
GLP	:	Yes

Test substance : R960002575
R960002575 is a code number for Starplex MPMG 2, which is a grease with the following composition

Wt % base oil	~80
Thickeners	
Li 12-hydroxy stearate	8.8%
Dilithium azelate	1.8%
Wt % other additives	~10

The test material was prepared as solutions in mineral oil at the following concentrations to achieve the desired dose levels.

Group	Dose group mg/kg/day	Concentration mg/ml	Volume ml/kg
I	0	0	2.1
II	525	250	2.1
III	1050	500	2.1
IV	2100	1000	2.1

Method : Male and female Sprague-Dawley rats aged 7 and 9 weeks respectively were used in this study.
The test material was applied to the shorn skin of groups of ten male and ten females at doses of 525, 1050 or 2100 mg/kg/day. Additionally, a group of ten male and ten females served as vehicle controls and for these animals mineral oil alone was applied. The test sites were covered with an occlusive dressing which was left in place for six hours. After this time, the dressings were removed and any residual test material was removed from the skin using a gauze and mineral oil. This treatment was continued daily, five days each week for 13 weeks.

Animals were observed twice daily for clinical signs of toxicity. A more thorough examination was undertaken weekly and this included a detailed physical examination for signs of local or systemic toxicity, pharmacological effects and palpation for tissue masses. Examination of the skin for irritation was undertaken pre-test and then daily during the first week of exposure and weekly thereafter.
Body weights and food intakes were recorded weekly.
At the end of the study, and after overnight fasting, animals were killed and blood samples were collected for the following hematological and serum chemistry investigations.

Hematology
Hemoglobin concentration
Hematocrit
Erythrocyte count
Platelet count
Mean corpuscular volume
Mean corpuscular hemoglobin
Mean corpuscular hemoglobin concentration
Prothrobin time
Activated partial thromboplastin time
Total and differential leukocyte counts
Erythrocyte morphology
Reticulocyte count

Clinical chemistry

Aspartate aminotransferase
Alanine aminotransferase
Alkaline phosphatase
Blood urea nitrogen
Fasting glucose
Total protein
Albumin
Globulin (calculated)
A/G ratio (calculated)
Creatinine
Total bilirubin
Sodium
Potassium
Chloride
Calcium
Inorganic phosphorus
Gamma-glutamyl transferase

A complete post mortem examination was performed on all animals. This included an examination of the external surface and all orifices; the external surfaces of the brain and spinal cord; the organs and tissues of the cranial, thoracic, abdominal and pelvic cavities and neck; and the remainder of the carcass.

The following organs were weighed:
Adrenal glands, brain, kidneys, testes with epididymides, liver and ovaries.

The following tissues were preserved and processed for histological examination.
Adrenal glands (2)
Aorta
Bone (sternum/femur with articular surface)
Brain (medulla/pons, cerebrum and cerebellum)
Epididymis (2)
Esophagus
Eye with optic nerve*
Heart
Kidneys (2)
Large intestine (cecum, colon and rectum)
Lacrimal gland*
Liver (2 sections)
Lung with mainstem bronchi
Lymph node (mediastinal)
Lymph node (mesenteric)
Mammary gland*
Muscle (biceps femoris)*
Nasal turbinates
Nerve (sciatic)
Ovaries (2)
Pancreas
Pituitary
Prostate
Salivary gland (submaxillary)
Seminal vesicles
Skin (treated and untreated)
Small intestine (duodenum, ileum and jejunum)
Spinal cord (cervical, thoracic, lumbar)*

Spleen
Stomach
Testes
Thymic region
Thyroid (with parathyroids)
Trachea
Urinary bladder
Uterus (body/horns with cervix)
Zymbal's gland*
Macroscopic lesions
Target organs
All the above tissues from all the animals in the high dose group and the controls were examined microscopically, except those indicated * which were preserved but not examined.

Statistical analysis
Body weight, body weight change from week 0, food consumption, hematology and clinical chemistry parameters, terminal organ and body weights and organ/body weight ratios and organ/brain weight ratios were analyzed. Mean values of all dose groups were compared to control at each time interval.
A Bartlett's test was performed to determine if groups had equal variance. If the variances were equal, parametric procedures were used; if not nonparametric parametric procedures were used.

The parametric procedures were the standard one way ANOVA using the F distribution to assess significance. If significant differences among the means were indicated, Dunnett's test was used to determine which means were significantly different from control. If a nonparametric procedure for testing equality of means was needed, the Kruskal-Wallis test was used, and if differences were indicated a summed rank test (Dunn) was used to determine which treatments differed from control.

A statistical test for trend in the dose levels was also performed. In the parametric case, standard regression techniques with a test for trend and lack of fit were used. In the nonparametric case Jonckheere's test for monotonic trend was used.

The test for equal variance (Bartlett's) was conducted at the 1% two-sided risk level. All other statistical tests were conducted at the 5% and 1%, two-sided risk level.

Result **:** There were no treatment-related deaths and there were no clinical signs of toxicity throughout the study. Although mild skin irritation was seen sporadically, it was not regarded as treatment-related. There were no treatment-related changes seen in the ophthalmoscopic examinations.
Apart from the mid dose males there were no treatment-related effects on body weight. In the case of the mid dose males, they were slightly lower than the controls throughout, but since animals in the higher dose group were unaffected this finding is not considered toxicologically significant.
Food consumption was unaffected by exposure to test material.
There were no biologically significant effects on either the hematology or clinical chemistry determinations that were undertaken.
Terminal organ weights, organ/body weight ratios and organ/brain weight ratios were unaffected by treatment.

There were no treatment-related macroscopic observations at necropsy and after histology, no microscopic changes were observed that were

considered to be treatment-related.

Reliability : (1) valid without restriction

(7)

Type : Sub-chronic
Species : Rat and Mouse
Sex : Male/female
Strain : Rat F344; Mouse B6C3F1
Route of admin. : oral feed
Exposure period : 90 days
Frequency of treatm. : Continual in the diet
Doses : 0.62, 1.25, 2.5, 5 & 10 % in the diet
Control group : Yes
Year : 1992
GLP : Yes
Test substance : Castor oil
USP AA grade castor oil was used.
It was incorporated in the diet and checks were made of actual dietary concentrations. These were as follows:

Target concentration (%)	Actual concentration (%)
0.62	0.62
1.25	1.26
2.5	2.64
5	4.91
10	9.67

Method : 10 animals of each sex and of each species were used for each dose group.
The treatment groups were fed diets containing 0.62, 1.25, 2.5, 5 or 10 % castor oil. In addition an extra 10 rats of each sex for each dietary level were fed for 21 days and these animals were used to provide blood samples for hematological and clinical chemical determinations on days 5 and 21, after which they were killed.
The main study animals were observed regularly throughout the study for clinical signs and were also weighed weekly. Food consumption was also recorded throughout the study.
At the end of the study at 13 weeks, all animals underwent a complete necropsy. Blood samples were taken for the following hematological and clinical chemical measurements.

Hematology: Red blood cell count, examination of red blood cell morphology, hematocrit, hemoglobin concentration, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell count, differential white cell count, reticulocyte count (absolute) and platelet count (absolute).

Clinical chemistry: alkaline phosphatase, albumin, urea nitrogen, creatinine, alanine aminotransferase activity, total bile acids, sorbitol dehydrogenase activity, total protein and creatinine kinase activity.

The following organs were weighed: liver, right kidney, right testicle, heart, thymus and lungs.

The following tissues were examined histopathologically in all control and

high dose rats and mice: Adrenal glands, brain, cecum, colon, duodenum, epididymis/seminal vesicles/prostate/testis or ovaries/uterus, esophagus, eyes (if grossly abnormal), femur (including marrow), heart, jejunum, kidneys, liver, lungs and mainstem bronchi, mammary gland, mandibular and mesenteric lymph nodes, nasal cavity and turbinates, pancreas, parathyroid glands, pituitary gland, preputial or clitoral glands, rectum, salivary glands, skin, spinal cord and sciatic nerve (if neurological signs present), spleen, forestomach and glandular stomach, thymus, thyroid gland, trachea, urinary bladder, Zymbal glands, all gross lesions and tissue masses including lymph nodes.
In addition the livers from male rats of all other dose groups were examined.

Reproductive toxicity screen
Sperm motility and sperm density was assessed at necropsy.
Additionally for the 12 days prior to necropsy, females were subject to a vaginal lavage with saline. The aspirate was stained and examined to enable an assessment to be made of the stages of the estrous cycle.

Statistical analysis
Body weight and organ weight data were examined within each sex by one-way analysis of variance followed by Dunnett's t-test if pair-wise comparisons were indicated ($P<0.05$).

Result : The following is taken from the abstract of the report:

Exposure to castor oil at dietary concentrations as high as 10% in 13-week studies did not affect survival or body weight gains of rats or mice (10 per sex and dose). There were no biologically significant effects noted in hematologic analyses in rats. Mild increases in total bile acids and in serum alkaline phosphatase were noted at various times during the studies in rats receiving the higher dietary concentrations of castor oil. Liver weights were increased in male rats receiving the 10% dietary concentration and in male and female mice receiving diets containing 5% or 10% castor oil. However, there were no histopathologic lesions associated with these liver changes, nor were there any compound-related morphological changes in any organ in rats or mice. No significant changes were noted in a screening for male reproductive endpoints, including sperm count and motility, and no changes were observed in the length of estrous cycles of rats or mice given diets containing castor oil. Thus, no significant adverse effects of castor oil administration were noted in these studies.

Reliability : (1) valid without restriction

(10)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Ames test
Result : Negative

Remark : A cosmetic ingredients review panel concluded that magnesium stearate was not a mutagen in microbial tests with Salmonella typhimurium TA-1535, TA-1537, TA-1538 and Saccharomyces cerevisiae D4 with or without metabolic activation by liver and lung preparations from rats, mice and monkeys.
The panel cited the following as the sources of the information:
FASEB (1976) and Litton Bionetics (1976)

Reliability : (4) not assignable
Information taken from a review report. No actual data are given.
(3) (9)

5.7 CARCINOGENICITY

Species	:	Mouse
Sex	:	Male/female
Strain	:	C3H
Route of admin.	:	Dermal
Exposure period	:	104 weeks
Frequency of treatm.	:	Twice weekly for 104 weeks
Doses	:	50 mg/application
Result	:	Negative
Control group	:	Yes
GLP	:	Yes
Test substance	:	PARL-3093-GR-81 PARL-3093-GR-81 is the code number assigned to a sample of Molytex EP-2. MolyteX EP-2 is a grease with the following composition

Base oil	approx	80% wt
Li 12-hydroxystearate		7.5% wt
Other additives	approx	12% wt

Method : 50 mg undiluted test material was applied twice weekly to the shorn interscapular region of 50 male and 50 female C3H mice aged 6-8 weeks. Positive control groups of 50 mice of each sex had 50 mg of a 0.05% solution of BaP in toluene applied twice weekly and these groups served as the positive controls. In addition solvent control groups of 50 mice of each sex received twice weekly applications of 50 mg toluene and a further group of 50 mice of each sex were untreated. The latter groups comprised the solvent and untreated controls respectively.

Applications were continued for 104 weeks or until a horny lesion on the surface of the skin grew to 1 mm^3. The lesion was diagnosed as a papilloma and the week that it appeared was recorded. If the tumor grew rapidly, invaded surrounding tissues, or became ulcerated and/or necrotic, it was diagnosed as an "advanced tumor" and the week of the transition was recorded. If a tumor regressed, treatment was resumed and continued until the end of the study or until another papilloma developed. If no growth appeared before death, the animal was recroded as not developing a tumor. If however, a second neoplasm developed, the time of its appearance was used in the calculation of the average latency period for the group.

Animals were observed daily throughout the study for clinical signs of toxicity.
At the termination of treatment, all surviving animals were sacrificed.
A complete post mortem examination was carried out on all animals sacrificed at the end of the study and on all animals that either died or were killed during the study because they were moribund.
At the post mortem examination the size and location of all skin neoplasms was recorded. Skin including the neoplasms and any other lesions was removed and placed in fixative for subsequent histopathological examination. Subcutaneous lymph nodes from the neck, ancillary region

and groin areas were also removed from the same animals and prepared for subsequent microscopic examination. The chest, abdominal and cranial cavities were examined and all organs were removed and a note made of their gross appearance. Tissues from each organ were preserved for possible microscopic examination.
H & E sections of the skin and of the mammary glands were examined microscopically.

Result : The number of mice with histologically-confirmed tumors is shown in the following table.

No. Mice	No. mice with tumors Malignant	Benign	Latent period (weeks)
Untreated controls			
46 males	0	0	-
50 females	1	2	-
Toluene controls			
48 males	3	3	87
50 females	5	2	72
Grease			
47 males	0	2	67
50 females	1	0	82
BaP			
46 males	21	5	48
49 females	45	2	49

It was concluded that the test material was not a skin carcinogen.

Reliability : (2) valid with restrictions
It should be noted that this study was a study of skin carcinogenicity only.

(1)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species : Rabbit
Sex : Female
Route of admin. : Gavage
Frequency of treatm. : Single dose given
Doses : 2.5 mg/kg
Result : Negative
Year : 1967
GLP : No
Test substance : Vehicle containing 5.5% Magnesium stearate
The test substance was a vehicle used to coat pharmaceutical tablets. The coating had the following composition:

Polyethylene glycol	27.5 mg
Starch	34 mg
Talc	27.5 mg
Silicon dioxide	5.5 mg
Magnesium sulphate	5.5 mg

Result : The CIR report states:
Fourteen females received the vehicle per os at a dose of 2.5 mg/kg 70 hours post coitus whereas 13 females were given the same dose 192 hours post coitus. Compared with anomalies in the fetuses from 16 untreated mothers (12 of 112 offspring had anomalies) the vehicle containing 5.5% magnesium stearate induced anomalies in 9 out of 86 and 11 out of 90 fetuses respectively, thus demonstrating the absence of

teratogenic effect.

Source : Cosmetic Ingredient Panel review (1982)
Reliability : (4) not assignable
Information is taken from the report of a Cosmetic ingredient review panel. The material tested contained only 5.5% magnesium stearate and the method was inadequate for an evaluation of developmental toxicity.

(4)

Species : Various

Remark : Leonard et al reviewed information on the teratogenic effect of lithium compounds.
They comment that results have varied in intact animals. Whereas some authors have not demonstrated teratogenic effcects of lithium compounds, others have done so. The malformations reported have included reduced number and weight of the litter, more resorptions, wavy ribs and incomplete ossification.
These discrepancies might be due to a different sensitivity of the species and strains used, the stress of daily injections and/or differences in lithium concentrations present in serum during critical periods of development.

Lithium carbonate given to mice over several days yielding serum levels comparable to those in man treated for manic-depressive disorders did not show any effects, but six times higher doses caused malformations in the offspring. Chronic exposure to lithium at doses that produced serum levels of the same order as seen in patients was toxic but did not affect the entire litter nor was it teratogenic to individual embryos.

Many authors have reported that lithium causes congenital defects, especially of the cardiovascular system when given to women during the first trimester of pregnancy. As a result registers of "Lithium babies" have been set up. Up till now, analysis of the limited data have demonstrated an effect.

The authors conclude that the question of the possible teratogenicity of lithium remains open until further work is done.

Reliability : (4) not assignable

(8)

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